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Oral presentation

C3d Enhancement of Anti-Env Immunity Using Modified HIV-1 Envelopes

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Background

DNA vaccines expressing the HIV-1 envelope (Env) have been relatively ineffective at generating high-titer, long-lasting, immunity. Conjugating the molecular adjuvant, C3d, to HIV-1 Env enhances both humoral and cellular immunity.

Methods

BALB/c mice were vaccinated with DNA plasmids (weeks 0, 4, and 8) expressing wild-type or modified envelope proteins. Each Env immunogen was tested alone or conjugated to multiple copies of the molecular adjuvant, C3d. Both humoral and cellular immunity were analyzed.

Results

DNA vaccines expressing a fusion protein of the soluble human CD4 (sCD4) and the Env_{gp120} enhanced the immunogenicity of the expressed fusion protein only when conjugated to mC3d3. Monoclonal antibodies that recognize CD4-induced epitopes on Envgp120 efficiently bound to sCD4-gp120 or sCD4-gp120-$mC3d_3$. In addition, both molecules bound to cells expressing appropriate coreceptors in the absence of cell surface hCD4. Mice vaccinated with DNA plasmids expressing either gp120-$mC3d_3$ or sCD4-gp120-$mC3d_3$ elicited antibodies that neutralized homologous virus infection. However, the use of sCD4-gp120-$mC3d_3$-DNA elicited the highest titers of neutralizing antibodies that persisted after depletion of anti-hCD4 antibodies. Interestingly, only mice vaccinated with DNA expressing sCD4-gp120-$mC3d_3$ had antibodies that elicited cross-protective neutralizing antibodies. In a separate set of experiments, the unique sequence found in the crown of the V3 loop of the envelope from the CD4-independent isolate, $HIV\text{-}1_{R2}$, was used to elicit cross-clade neutralizing antibodies. The codons encoding for the V3 loop amino acids, Pro-Met, were introduced into the sequences encoding the $gp120_{ADA}$ (R5) or $gp120_{89.6}$ (R5X4). Mice vaccinated with $gp120_{ADA}$-$mC3d_3$-DNA with the Pro-Met mutation had antibodies that neutralized HIV-1 infection, but not the $gp120_{89.6}$-$mC3d_3$-DNA.

Conclusion

Therefore, the use of sequences that expose cryptic epitopes by CD4 or found in CD4-independent viral isolates expose neutralizing epitopes that can elicit broad, cross-clade immunity.